29. (New) A method for determining the phenotype of a test cell from a given tissue, comprising detecting the presence or absence of differential expression, relative to a normal cell of the given tissue type, of at least 25 different genes shown in Table 1,

wherein the presence of differential expression indicates that said test cell has an IBD or pre-IBD phenotype.--

REMARKS

Claims 5 to 7 are pending. Claims 5 and 6 have been amended, and new claims 19 to 29 have been added herein. Thus, claims 5 to 7 and 19 to 29 are presently under examination.

Regarding the amendments

The specification has been amended at page 51, line 7, to replace "*X. Exemplification*" with "Table 1." The specification also has been amended at page 46, line 28, to replace the reference to nucleic acids of SEQ ID Nos: 1-146 with "nucleic acids shown in Table 1." The amendments are supported throughout the specification by reference to Table 1, for example, at page 3, line 31, which refers to an IBD gene set shown in Table 1, and at page 19, lines 6-7, which indicates that Table 1 shows sequences which are over- or underexpressed in CD or UC derived cells relative to normal tissue.

Claim 5 has been amended in several respects. In particular, the preamble of claim 5 has been amended to recite

determining the phenotype of a "test cell from a given tissue." The amendment is supported throughout the specification, for example, at page 42, lines 25-34, which discloses determining the phenotype of a test cell "from a given human tissue." Claim 5 also has been amended to indicate that the recited differential expression is relative to a normal cell "of the given tissue type." This amendment is supported throughout the specification, for example, at page 42, lines 31-32, which discloses that differential expression can be determined by comparison to normal cells of the given tissue type.

Claim 5 additionally has been amended to indicate that the method is performed by detecting the presence or absence of differential expression of at least "5 different genes" shown in Table 1. The amendment is supported throughout the specification, for example, at page 3, lines 22-25, which discloses detecting transcripts of at least 5 different IBD genes of the disclosed IBD gene set. See, also, page 3, line 31, which indicates that the IBD gene set is shown in Table 1.

Claim 5 further has been amended to add a concluding phrase reciting that "the presence of differential expression indicates that said test cell has an IBD or pre-IBD phenotype." The amendment is supported throughout the specification, for example, at page 5, lines 29-34, which indicates that certain genes are differentially expressed in intestinal tissue of IBD patients compared with related normal cells and that the upregulation or downregulation of particular genes can be used to identify or classify IBD cells, and at page 42, lines 25-26,

which indicates that a phenotype can be normal or can be IBD or pre-IBD.

Claim 6 has been amended to more clearly indicate that the differential expression is upregulation or downregulation by at least a factor of two. The amendment is supported, for example, at page 15, lines 33-36, which indicates that differential expression refers to both upregulation and downregulation.

New claims 19 to 29 have been added herein. New claim 19 is directed to the method of claim 5 in which the test cell is an intestinal cell. New claim 19 is supported, for example, by claim 5 as originally filed and in the specification, for example, at page 2, lines 15-22, which discloses determining the phenotype of a cell of intestinal origin.

New claims 20, 21, 22 and 23 are directed to the method of claim 5 which involves detecting the presence or absence of, respectively, at least 10, 25, 50 or 75 different genes shown in Table 1. New claims 20 through 23 are supported throughout the specification, for example, at page 3, lines 22-25, which discloses detecting transcripts of at least 5, 10, 25, 50, 75, 100, 125 and 146 different IBD genes of the disclosed IBD gene set and at page 2, line 18, which equates the genes shown in Table 1 with the "IBD gene set."

New claim 24 is directed to the method of claim 5, which involves detecting the presence or absence of differential

expression of genes that belong to distinct functional classes. New claim 24 is supported throughout the specification, for example, at page 6, lines 25-28, which indicates that the genes shown in Table 1 were assigned to seven functional classes.

New claim 25 is directed to the method of claim 5, in which detecting the presence or absence of differential expression is performed using *in situ* hybridization. New claim 25 is supported throughout the specification, for example, at page 42, lines 17-19, which indicates that diagnostic methods can be performed using *in situ* hybridization.

New claim 26 is directed to the method of claim 5, in which detecting the presence or absence of differential expression is performed using hybridization to nucleic acid probes immobilized on a solid support. In new claim 27, the nucleic acid probes are immobilized in a two-dimensional array. New claims 26 and 27 are supported throughout the specification, for example, at page 45, lines 11-12 and 24-26, which indicates that diagnostic methods can be practiced using nucleic acid probes immobilized on a DNA chip in an organized array and that nucleic acid probes can be spotted onto a substrate in a two-dimensional matrix or array and hybridized to samples containing nucleic acids.

New claim 28 is directed to a method for determining the phenotype of a test cell from a given tissue by detecting the presence or absence of differential expression, relative to a normal cell of the given tissue type, of at least 5 different

genes shown in Table 1 and belonging to distinct functional classes, where the presence of differential expression indicates that the test cell has an IBD or pre-IBD phenotype. New claim 28 is supported by claim 5 as originally filed and by the portions of the specification supporting amendments to claim 5 discussed above. The aspect of new claim 28 relating to determining differential expression of genes belonging to distinct functional classes is supported in the specification, for example, at page 6, lines 25-28, which discloses that the genes shown in Table 1 were assigned to seven functional classes.

New claim 29 is directed to a method for determining the phenotype of a test cell from a given tissue by detecting the presence or absence of differential expression, relative to a normal cell of the given tissue type, of at least 25 different genes shown in Table 1, where the presence of differential expression indicates that the test cell has an IBD or pre-IBD phenotype. New claim 29 is supported by claim 5 as originally filed, by the portions of the specification supporting amendments to claim 5 discussed above, and in the specification, for example, at page 2, lines 15-18, which discloses that a method of the invention for determining the phenotype of a cell can be practiced by determining differential expression of at least 25 different genes shown in Table 1 (the "IBD gene set").

As set forth above, each of the amendments and new claims is supported in the application as originally filed and does not add new matter. Applicant therefore respectfully requests entry of the amendments and new claims.

Regarding the Declaration

The Office Action indicates that the Declaration is defective for failing to indicate the inventor's citizenship. A substitute Declaration is submitted herewith in accordance with 37 C.F.R. 1.67(a) indicating the inventor's country of citizenship. Applicant therefore respectfully requests that this ground for objection be withdrawn.

Regarding informalities in the specification and claims

The Examiner objects to the specification for referring to Table 1 and SEQ ID NOS: 1 to 146 without labeling Table 1 or listing sequences in the application. The Examiner further objects to claim 5 for depending on canceled claim 1.

The specification has been amended such that, at page 46, the reference to "SEQ ID NOS: 1 to 146" has been replaced with a reference to the sequences "shown in Table 1." Furthermore, the specification has been amended at page 51 such that the reference to "X. Exemplification" has been replaced with "Table 1." Claim 5 also has been amended herein to independent form. In view of the amendments, Applicant respectfully requests that the objection to the specification and to claim 5 be withdrawn.

Rejection Under 35 U.S.C. 112, first paragraph

Applicant respectfully traverses the rejection of claims 5 to 7 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor had possession of the claimed invention at the time the application was filed. Specifically, it is alleged that the Applicant was not in possession of the genes involved in IBD and that Table 1 does not include any gene sequences.

Applicant submits that the specification provides sufficient written description for the full scope of the invention. In particular, Table 1 of the specification recites more than 140 genes which are differentially expressed and can be useful in the claimed methods for determining the phenotype of a test cell. Furthermore, Table 1 identifies the individual genes with their GenBank Accession number, thus placing those of skill in the art in possession of the relevant gene sequences. Applicant notes that an accession number from GenBank is commonly used as a preferred method of referencing DNA and amino acid sequences in scientific publications and that the public availability of the GenBank database places the referenced genes in the possession of those skilled in the art. Applicant respectfully submits that such an accession number is a "precise definition" that is sufficient to distinguish each of the referenced nucleic acid sequence from other sequences. In view of the above remarks, the specification clearly provides sufficient written description for the full scope of the claimed invention. Accordingly, Applicant respectfully requests that the

Examiner remove the rejection of claims 5 to 7 under the first paragraph of 35 U.S.C. § 112.

Rejection Under 35 U.S.C. § 112, second paragraph

The rejection of claims 5 to 7 under 35 U.S.C. 112, second paragraph, as allegedly incomplete for omitting essential steps, is respectfully traversed. In rejecting the claims, the Office Action asserts that the claimed methods do not recite how or which phenotype of the cell is determined and that the relationship of the phenotype and the patient's risk of having IBD is omitted.

Regarding the phrase "phenotype of a cell"

Claim 5 stands rejected due to an alleged lack of clarity of the phrase "phenotype of a cell." Specifically, it is queried whether Applicant means physical changes of a cell, or that the method uses external markers etc.

Applicant submits that claim 5 is clear and definite as written. In particular, the term "phenotype" is well known in the art to mean anything that is part of the observable structure, function, or behavior of a living organism. To more clearly indicate the claimed subject matter, claim 5 has been amended to add a concluding phrase which indicates that the presence of differential expression indicates that the test cell has an IBD or pre-IBD phenotype. Thus, it is clear that the phrase "phenotype of a test cell" refers to those phenotypic

characteristics that distinguish an IBD cell or pre-IBD cell from a normal cell. In view of the above remarks and amendments, Applicant respectfully requests that the Examiner remove this ground for rejection.

Regarding the phrase "particularly intestinal origin"

Claim 5 also stands rejected as allegedly indefinite in view of the phrase "particularly intestinal origin." While Applicant maintains that claim 5 is clear and definite as written, this phrase has been deleted by the present amendment. Applicant therefore respectfully requests that this ground for amendment be removed.

Regarding the phrase "relative to a normal cell"

Claim 5 further stands rejected as allegedly vague and indefinite due to the phrase "relative to a normal cell." In this regard, the Office Action indicates that it is unclear whether "normal cell" refers to any normal cell or only an intestinal tissue cell.

Applicant submits that claim 5 is clear and definite as written and that, in view of the specification, one skilled in the art understands that the recited "normal cell" is any appropriate control cell. In this regard, the specification teaches, for example, that, in determining the phenotype of a test cell from a given human tissue, expression is compared to a level of expression in normal cells of the given tissue type.

While Applicant submits that the claim is clear and definite as written, claim 5 has been amended to recite a normal cell "of the given tissue type" in order to further prosecution. In view of the above, Applicant respectfully requests that the Examiner remove this ground for rejection.

Regarding claim 6

Claim 6 stands rejected as allegedly unclear due to insufficient antecedent basis for "the assay." In view of the amendment of claim 6 herein to delete the term "the assay," Applicant respectfully requests that this ground for rejection be removed.

As set forth above, each of the claims are clear and definite as written. Accordingly, the Examiner is respectfully requested to remove the rejection of claims 5 to 7 under the second paragraph of 35 U.S.C. § 112.

Rejections Under 35 U.S.C. 102(b)

§102(b) Rejection over Puolakkainen et al.

The rejection of claims 5 to 7 under 35 U.S.C. 102(b) as allegedly anticipated by Puolakkainen et al., Gastroenterology 114: page A1064 (1998), respectfully is traversed.

Independent claim 5 is directed to a method for determining the phenotype of a test cell from a given tissue by

detecting the presence or absence of differential expression, relative to a normal cell of the given tissue type, of at least 5 different genes shown in Table 1, where the presence of differential expression indicates that the test cell has an IBD or pre-IBD phenotype. According to MPEP § 2131, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). In the present case, Puolakkainen et al. do not disclose each and every element of the claimed invention.

In particular, Puolakkainen et al. do not teach determining the phenotype of a test cell by detecting the presence or absence of differential expression and, therefore, cannot anticipate the invention. At best, Puolakkainen et al. characterize the expression of four genes (stromelysin-2 (MMP-10); collagenase-3 (MMP-13); macrophage metalloelastase (HME, MMP-12); and tissue inhibitor of metalloproteases (TIMP)) in samples from UC and CD patients and in ischemic colitis and normal intestine samples. Thus, Puolakkainen et al. characterize up- or down-regulation of gene expression in cells of a known phenotype but do not teach determining the phenotype of a test cell based on differential expression as claimed. Absent such a teaching, the cited reference by Puolakkainen et al. cannot anticipate the invention.

Puolakkainen et al. further cannot anticipate the invention since the cited reference does not teach detecting the presence or absence of differential expression of at least five different genes shown in Table 1, as recited in independent claim 5. Since the cited reference does not teach this element of the claims, it further cannot anticipate the claimed invention. Accordingly, Applicant respectfully requests that the Examiner remove the rejection of claims 5 to 7 under 35 U.S.C. § 102(b) as allegedly anticipated by Puolakkainen et al.

§102(b) Rejection over Alexander et al.

The rejection of claims 5 and 6 under 35 U.S.C. 102(b) as allegedly anticipated by Alexander et al., Digestive Disease and Sciences 41:660-669 (1996), respectfully is traversed. The Office Action indicates that Alexander et al. anticipate the claimed invention, asserting that Alexander et al. describe determining altered expression of protooncogenes in patients with inflammatory bowel disease as compared to expression in normal colon epithelial cells.

Alexander et al. do not teach each and every element of the claims and, thus, cannot anticipate the claimed invention. Firstly, Alexander et al. cannot anticipate the invention since the cited reference does not teach determining the phenotype of a test cell by detecting the presence or absence of differential expression as required in the claimed methods. At best, Alexander et al. characterize expression of several protooncogenes, including *H-ras, c-myc, c-fos, c-jun, junB, -myc,*

c-abl, c-yes, and *p53* in colonic epithelial cells of patients and controls. While the cited reference appears to characterize up- or down-regulation of several protooncogenes in cells of a known phenotype, this reference does not teach determining the phenotype of a test cell as claimed. Thus, claims 5 and 6 are novel over the cited publication by Alexander et al.

Secondly, Alexander et al. do not teach detecting the presence or absence of differential expression of at least 5 different genes shown in Table 1, as in the methods of claims 5 and 6. Absent such a teaching, the cited reference by Alexander et al. further cannot anticipate the claimed invention. For these reasons, Applicant respectfully requests that the Examiner remove the rejection of claims 5 and 6 under 35 U.S.C. 102(b) as allegedly anticipated by Alexander et al.

§102(b) Rejection over Dieckgraefe et al.

The rejection of claims 5 to 7 under 35 U.S.C. 102(b) as allegedly anticipated by Dieckgraefe et al., Digestive Disease and Sciences 114:G3954 (1998), respectfully is traversed.

The Office Action indicates that Dieckgraefe et al. use a GeneChip expression monitoring system to examine mucosal gene expression in ulcerative colitis, Crohn's disease and non-IBD specimens. The Action further indicates that Dieckgraefe et al. observe dramatic changes in the expression of a wide range of genes, and that genes were identified that appear to be specific

markers for specific diagnosis, disease activity and particular features of histology.

Applicant submits that the cited reference cannot anticipate the claimed invention since it does not teach all elements of the claimed invention. Firstly, Dieckgraefe et al. at best describe a process for identifying and cataloging of molecules expressed in the context of mucosal inflammation. However, despite any such identification, Dieckgraefe et al. do not describe determining the phenotype of a test cell of unknown phenotype by detecting the presence or absence of differential expression of a gene relative to an normal cell. Absent such a teaching, Dieckgraefe et al. cannot anticipate the invention. Secondly, Dieckgraefe et al. appear to report general classes of genes in which differential expression was observed. Yet the cited reference does not teach detecting the presence or absence of at least 5 different genes shown in Table 1 of the subject application and, thus, further cannot anticipate the claimed invention. For these reasons, Applicant respectfully requests that the Examiner remove the rejection of claims 5 to 7 under 35 U.S.C. § 102(b) over Dieckgraefe et al.

§103 Rejection over Alexander et al.

The rejection of claims 5 to 7 under 35 U.S.C. § 103 as allegedly obvious over Alexander et al. is respectfully traversed. As discussed above, Alexander et al. appear to assay for altered expression of protooncogenes such as *H-ras, c-myc, c-fos, c-jun, junB, N-myc, c-abl, c-yes,* and *p53* in patients with

inflammatory bowel disease as compared to expression in normal colon epithelial cells. The cited reference principally relates to establishing changes in gene expression relevant to the increased risk of colon cancer in patients with inflammatory bowel disease.

Applicant submits that the claimed invention is unobvious over the cited reference by Alexander et al. The cited reference seeks to establish whether altered protooncogene expression is relevant to development of colon cancer in patients with inflammatory bowel disease. However, this reference does not teach or suggest at least five different genes shown in Table 1 of the subject application, or using differential expression of such genes to determine the phenotype of a test cell. Absent such teachings or suggestions, the claimed methods are unobvious over the cited reference.

In view of the above remarks, Applicant respectfully requests that the Examiner remove the rejection of claims 5 to 7 under 35 U.S.C. § 103 as allegedly obvious over Alexander et al.

CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he/she is invited to call the undersigned agent or Cathryn Campbell .

Respectfully submitted,

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Date

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APPENDIX A

Paragraph spanning pages 46 and 47:

In yet another embodiment, the invention provides methods for determining whether a subject is at risk for developing a disease, such as a predisposition to develop IBD, for example UC or CD, associated with an aberrant activity of any one of the polypeptides encoded by nucleic acids **shown in Table 1 [of SEQ ID Nos: 1-146]**, wherein the aberrant activity of the polypeptide is characterized by detecting the presence or absence of a genetic lesion characterized by at least one of (i) an alteration affecting the integrity of a gene encoding a marker polypeptides, or (ii) the mis-expression of the encoding nucleic acid. To illustrate, such genetic lesions can be detected by ascertaining the existence of at least one of (i) a deletion of one or more nucleotides from the nucleic acid sequence, (ii) an addition of one or more nucleotides to the nucleic acid sequence, (iii) a substitution of one or more nucleotides of the nucleic acid sequence, (iv) a gross chromosomal rearrangement of the nucleic acid sequence, (v) a gross alteration in the level of a messenger RNA transcript of the nucleic acid sequence, (vii) aberrant modification of the nucleic acid sequence, such as of the methylation pattern of the genomic DNA, (vii) the presence of a non-wild type splicing pattern of a messenger RNA transcript of the gene, (viii) a non-wild type level of the marker polypeptide, (ix) allelic loss of the gene, and/or (x) inappropriate post-translational modification of the marker polypeptide.

At page 51, line 7, "X. Exemplification" has been deleted and replaced with --Table 1.--

In the claims

5. (Amended) A method for determining the phenotype of a **test** cell **from a given tissue**, **[particularly a cell of intestinal origin,]** comprising detecting the **presence or absence of** differential expression, relative to a normal cell **of the given tissue type**, of at least **5 different genes** **[** one gene **]** shown in Table 1 **[** (herein the "IBD gene set"), or other IBD genes identified according to the method of claim 1 **]**, **wherein the presence of differential expression indicates that said test cell has an IBD or pre-IBD phenotype**.

6. (Amended) The method of claim 5, wherein **said differential expression is upregulation or downregulation by** **[** the assay detects a difference in the level of expression of an IBD gene of **]** at least a factor of two.